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CERMAK & KENEALY LLP
ACS LLC
515 EAST BRADDOCK ROAD
SUITE B
ALEXANDRIA, VA 22314

EXAMINER	
ROBINSON, HOPE A	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/716,480
Filing Date: November 20, 2003
Appellant(s): GUNJI

Shelly Guest Cermak
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 15, 2005.

EXAMINER'S ANSWER

(1) Real Party in Interest

This is in response to appellant's brief on appeal filed December 15, 2005. A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct. However, the brief did not indicate that the claims on appeal are listed in the Appendix.

(4) Status of Amendments After Final

The appellant's statements of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that all the claims stand or fall together.

(8) Claims Appealed

Claims on appeal have been presented correctly.

(9) Prior Art of Record

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 112 reads as follows:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-4 and 6-7 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for a DNA of SEQ ID NO:1, in which a mutation results, said mutation being a glycine residue at position 56 is replaced by serine, does not reasonably provide enablement for the genus of any DNA that encodes a mutant LysE protein of a coryneform bacteria. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The instant claims are drawn to a DNA that encodes a mutant LysE protein, which imparts resistance to a L-lysine analogue when introduced into a methanol-assimilating bacterium, and to a bacterium into which said DNA has been introduced. The ability to make all DNAs that encode mutant LysE protein included in the scope of these claims would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification teaches SEQ ID NO: 1, a DNA encoding *C. glutamicum* wild-type LysE protein, in which glycine residue 56 is mutated to a serine (G56S), and the DNA encoding the G56S mutant of SEQ ID NO:2, the *C. glutamicum* wild-type LysE protein. The art fully enables a mutant of SEQ ID NO: 1, whereby glycine 56 is mutated to serine in the encoded LysE protein, and any DNA encoding the G56S mutant of SEQ ID NO:2 based on the degeneracy of the genetic code; yet, the art includes no

examples of *C. glutamicum* mutant LysE protein encoding genes. While the instant specification describes and enables means for identifying other mutant LysE encoding genes using *in vitro* mutation, introduction of the DNA into *Methylophilus methylotrophus*, and selection on S-(2-aminoethyl)cysteine containing media, etc., these methods do not enable one of skill in the art to make all, or a relevant portion of, the nucleotides and polynucleotides within the scope of the claims. The ability to find a mutant LysE encoding gene, which is structurally related to SEQ ID NO:1 and functionally related to mutant G56S, is not equivalent to the ability to make a mutant LysE encoding gene as required by the statute (i.e., "make and use"). No description in the specification or the art provides particular residues whose encoding is important within the disclosed sequence so that its mutant LysE-nature is maintained except for amino acid residue glycine 56. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope.

(11) Arguments:

Response to Arguments

Appellants on page 5 (second paragraph) opine that the rejection of record cannot be maintained because the specification is fully enabled as every mutation encompassed by the claims is not explicitly exemplified by the specification and one of skill in the art would be able to determine those mutations that fall within the scope of the claims via routine experimentation. The Appellants further state that "[I]t is well

established in the case law that enablement is not precluded even if some experiment is necessary, although the amount of experimentation needed must not be unduly extensive', (see page 6 (first paragraph)". It is also stated that 'inoperable embodiments are permitted, as long as one skilled in the art is not required to experiment unduly to practice the claimed invention (page 6 of the Brief). The Appellants acknowledge that some experimentation will be necessary to determine variants of the DNA which encodes a protein having not more than 10 amino acid residues, at positions other than the 56th residue, substituted, deleted or inserted, however, state that such experimentation is not undue but merely routine for the person of ordinary skill in the art.

The Appellant's arguments have been considered, however, are not persuasive. Appellants have amended the claims to be drawn to the genus of any DNA that encodes a mutant LysE protein of a coryneform bacteria in which the glycine residue at position 56 is replaced with another amino acid residue, and not more than 10 amino acid residues at positions other than the 56th residues are varied, wherein said mutant impart resistance to S-(2-aminoethyl-cysteine) in a methylotroph (emphasis added). Appellants argue that one of ordinary skill in the art would be enabled to make and use the invention as claimed in light of the specification and knowledge in the art concerning the LysE protein and state that sequence alignments are provided in Appendix B as support. However, the issue in the rejection is whether the 10 amino acid residues other than the 56th residue that are substituted, deleted or inserted will in fact retain the function ascribed to the protein. The critical aspect of the issues presented in the office action of record is undue experimentation (make and test) and unpredictability

(unpredictable what part of the structure is responsible for function) as analyzed by the Wands factors.

Predictability of which changes can be tolerated in a protein's amino acid sequence to obtain a desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions as are claimed herein. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, because certain positions in the sequence are critical to the protein's structure/function relationship.

It is known in the art that an amino acid change can destroy the function of the protein in many cases. For example, various sites directly involved in binding activity, oligomerization, active site catalysis and the three-dimensional structure can be affected. No correlation is made between structure and function for the variants encompassed in the claims. The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of the variant sequences that are encompassed by

the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, insertions, etc., in the disclosed sequence would result in a protein having activity comparable to the one disclosed. As plural substitutions are introduced, their interactions with each other and their effects on the structure and function of the protein increase exponentially and are unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the variants encompassed in the claims would retain the recited function/activity.

Although there is no direct prior art related to the instant claims, the prior art generally acknowledges that a structural change in a protein's sequence can and often does affect the function of the protein. The art recognizes that a single amino acid change have a significant functional impact on the polypeptide. Therefore, the substitutions contemplated within SEQ ID NO:2 can result in an unstable product, rendering the invention unpredictable. Another issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. Although the instant specification describes and enables methods for identifying other mutant LysE encoding genes using *in vitro* mutation, introduction of the DNA into *Methylophilus methylotrophus*, and selection on S-(2-aminoethyl)cysteine containing media, these methods do not enable one of skill in the art to make all, or a relevant portion of, the nucleotides and polynucleotides within the scope of the claims. The ability to find a mutant LysE encoding gene, which is structurally related to SEQ ID NO:1 and functionally related to mutant G56S, is not

equivalent to the ability to make a mutant LysE encoding gene as required by the statute (i.e., "make and use"). The description in the specification and the art is devoid of particular residues whose encoding is important within the disclosed sequence so that its mutant LysE-nature is maintained except for amino acid residue glycine 56. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. While recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity. This is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited. Therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

On page 7 of the Brief the Appellants state that Appendix B provides evidence that supports the claimed variants. The alignment provided is presumed to correspond to the claimed product in the invention (see page 7 of the Brief, second paragraph). The alignment provided is not representative of the entire genus encompassed in the claimed invention and merely represents sequences that have some homology to the claimed sequence. Accurate predictions of a protein's function from mere sequence data are limited. Sequence homology does not indicate where in a sequence all the variants encompassed in the claims can be made or predict function. The appellants state that the alignment provided shows that glycine at position 56 is conserved. Appellants are arguing a limitation not evidenced by the present claim language. Note that the claims are directed to SEQ ID NO:2 except that the glycine residue at position 56 is replaced with another amino acid residue and not more than 10 amino acid residues at positions other than the 56^{th} residue are substituted, deleted or inserted.

The language of the claim is contrary to Appellant's statements as no conserved region is identified. The broadest reasonable interpretation of the claims is: any 10 residues at any positions other than position 56 in the sequence can be deleted; any 10 residues at any positions other than position 56 and position 56 in the sequence can be subjected to substitutions and any 10 residues at any positions other than position 56 can be inserted. Additionally, the claim language can be interpreted as 11 residues in SEQ ID NO:2 (which has 236 residues) can be substituted with any of the 20 naturally occurring amino acids or any of the unspecified amount of unnaturally occurring amino acids. The specification on pages 30-31 provide exemplification of a serine residue

replacing glycine at position 56 and a few other point mutations. However, there is no indicia of a sequence having residue 56 replaced with for example a proline and 10 other residues contiguously deleted or deleted throughout the sequence and retaining activity. The permutations encompassed in the claims are enormous as the claim encompasses one to ten deletions alone; one to ten insertions alone; one to ten substitutions alone; deletions and insertions; deletions, insertions and substitutions; deletions and substitutions; and insertions and substitutions. The rejection of record indicates that the claimed invention is not commensurate in scope with the claims. Appellant is enabled for the species exemplified for example on pages 30-31 of the instant specification; however, the claims encompass a large variable genus not supported by the instant specification. The number of possible naturally-occurring amino acid sequence variation contemplated relative to a 236 amino acid reference sequence, where all differences between the possible sequences and the reference sequence are only substitutions, can be calculated by the following formula for combinatorials:

$$N = \frac{X^n L!}{n!\,(L-n-1)!}$$

where 'N' is the number of possible sequences, 'X' is the number of different residues that can be substituted for a residue in the reference sequence (in our case 19 amino acid residues), 'L' is the length of the reference sequence and 'n' is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence. In the instant case, the number of possible variants resulting from substitutions only is:

$$N=\frac{19!x236!}{1!\,(236-1-1)!}=1.7x10^{32}.$$

The figure $1.7x10^{32}$ only considers single, natural amino acid substitutions and not nearly the entire scope of the claim. Thus it is clear that while on its face "not more than 10" substitutions, deletions and insertions appear to be a reasonable small number; in actuality it is more mutants than are testable routinely. To put the situation in perspective, testing one peptide per second would take $5.4x10^{24}$ years, which exceeds the existence of the earth. Undue experimentation would be required to construct and test $1.7x10^{32}$ variants resulting solely from substitutions; first round of testing would be for being classified as a LysE protein and then for the specific activity claimed. Note that the figure above does not encompass deletions or insertions or combinations of all three. Thus it is clear that sufficient guidance, working examples and predictability is required to enable the full extent of the claimed scope. Hence undue experimentation is required by the claimed invention. Further appellant's statement that the experimentation involved is routine is merely an assertion that has not been substantiated by evidence. Appellants are reminded that, "Argument of counsel cannot take the place of evidence lacking in the record." *In re Scarbrough*, 182 USPQ 298, 302 (CCPA 1974). The instant specification is absent guidance/direction as to conserved regions or domains or motifs. No guidance is provided as to what amino acids are to be substituted, deleted or inserted in the recited up to 10 amino acids. No guidance is provided as to where in the proteins sequence said modifications can be tolerated or what combinations will occur for example, substitutions with insertions and deletions or

substitutions only etc. Furthermore, following construction of the enormous amount of variants, there is a requirement to test the same for belonging to the LysE family and for a specific activity. It is in no way predictable to alter a protein's structure and obtain the activity of the native/wild-type protein and such an exercise would require undue experimentation absent guidance/direction such as identification of motifs or conserved regions or information regarding the protein's tolerance to modification.

On pages 8-9 of the Brief, appellants state that the cited alignments provide support for the claimed embodiments and state that "many factors must be considered when evaluating the enablement of claim scope....one must look at the support provided in the specification...one must also look at the state of the art at the time of the invention. It is further stated that "Knowledge of these sequences provides a wealth of structure-function relationship information, and combined with the information provided in the specification clearly provides sufficient structure-function information to allow one of skill in the art to determine other mutational species of these proteins which will retain the claimed function, particularly when the variance permitted by the claim is so small". Appellants conclude that "...one of skill in the art would be able to choose and determine through routine experimentation which mutants possess the claimed activity". Appellant's comments are noted but are not persuasive as the homology data provided in Appendix B is not representative of the genus encompassed in the claims, nor does it provide guidance missing from the instant specification as to how to make and test the encompassed variants in the claims nor does it indicate the specific activity claimed by correlating structure with function. It simply provides a sequence homologous to a

member of the LysE family, however, does not specifically provide one of the variants claimed or provide information as to what the $1.7x10^{32}$ substitutions encompassed in the claims will look like or provide information as to whether the specific activity claimed is retained.

The appellant's arguments have been considered and have been fully addressed, however, are not persuasive.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

HOPE ROBINSON
PATENT EXAMINER

Examiner Hope Robinson

February 21, 2006

Conferees:
Jon P. Weber

JON WEBER
SUPERVISORY PATENT EXAMINER

Kathleen Kerr

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER

CERMAK & KENEALY LLP
515 EAST BRADDOCK ROAD, STE. B
ALEXANDRIA, VA 22314